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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,636	08/03/2001	Manfred Mutter	2548-17	5241

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/890,636	Applicant(s) Mutter
	Examiner David Lukton	Art Unit 1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Dec 2, 2002 .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-6 is/are pending in the application.

4a) Of the above, claim(s) 5 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-4 and 6 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 11
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Pursuant to the directives of paper No. 10 (filed 12/2/02), claims 1-4 and 6 have been amended. Claims 1-6 remain pending; claim 5 remains withdrawn from consideration. Applicants' arguments filed 12/2/02 have been considered and found not persuasive.

*

Claims 1-4 and 6 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 1, last two lines recites the following: "...a...polymer, possibly bound". Here, *optionally* would be better than "possibly".
- Claim 1 recites the following:

  "a residue of a water-soluble polymer, possibly bound to a spacer group".

  First, since this is the last member of the Markush Group, this phrase should be preceded by the conjunction "or", or else the conventional "selected from the group consisting of" language should be adopted. Second, the term "bound" could encompass both covalent and non-covalent bonding; if covalent bonding only is intended, then the term *bonded* would be better. In addition, the term *optionally* is preferable to "possibly". Following is one option for claim language:

  ...or R^1 and R^2 each independently denotes a water-soluble polymer, wherein said polymer is optionally bonded to the carbon bearing R^1 and R^2 via a spacer group.

  Another option would be to create two new substituent variables (e.g., "X" and "L") and to adopt the following language:

...or R^1 and R^2 each independently denotes a group X-L-, wherein X is a water-soluble polymer, and L is a covalent bond or a spacer moiety.

- Each of claims 3, 4 and 6 recites the following: "wherein it is derived". Use of the word "it" creates a degree of indefinitness, and is grammatically suboptimal. Using claim 3 as an example, the following would be better:
The derivative according to claim 1 which is derived from a cyclosporin in which...

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 6 are rejected under 35 U.S.C. §102(b) as being anticipated by Wohr (*J. Am. Chem. Soc.* **118**, 9218, 1996).

As indicated previously, Wohr discloses (Scheme I, page 9219) a compound designated Xaa($\Psi^{R',R"}$ pro), and its incorporation into various peptides. The cited claims are anticipated, since there are no limits on what the term cyclosporin "derivative" might encompass.

In response, applicants have argued that Wohr only suggests the compound Xaa($\Psi^{R',R"}$ pro) for use as a synthetic intermediate. Whether true or not, the instant claims do not preclude synthetic intermediates. Applicants have also observed that Wohr has incorporated the

Xaa($\Psi^{R',R"}$ pro) moiety into three different peptides; applicants have questioned the relevance of this disclosure on the basis that Wohr provides no biological data on these peptides. While this may be true, the instant claims do not require the claimed compounds to exhibit any particular biological activity. Next, applicants argue that Wohr provides no suggestion to use the Xaa($\Psi^{R',R"}$ pro) moiety in the synthesis of cyclosporins. However, this is also not a requirement of the instant claims. Rather, what is required by the instant claims is that one take possession of a compound which is in some manner or form could be construed as a "derivative" of cyclosporin, however remote the relationship.

Next, applicants attribute to the examiner an assertion that a skilled chemist would be unable to differentiate cyclosporin from a "regular peptide". The examiner has made no such assertion. The issue pertains to the question of where the dividing line might be between a compound that is a derivative of cyclosporin, and a compound that is not.

Next, applicants argue that "regular peptides" are synthesized by a ribosomal pathway, whereas cyclosporins are produced by microorganisms. The validity of this depends on how one might wish to define the term "regular peptides", but this particular argument is left unchallenged. Next, applicants argue that for a compound to be considered to be a "cyclosporin", the compound must contain at least one amino acid which is methylated on an amide group, and that the compound must contain at least one D-amino acid, and that there may be other amino acids which are not genetically encoded by eukaryotic organisms.

This particular point is also left unchallenged. Next, applicants point to the index of a book which fails to list cyclosporins. However, this omission has no relevance to any of the issues under consideration; authors cannot cover all topics and must make choices.

It is evident from the foregoing, that applicants have misunderstood the examiner's position. The question is not whether Wohr discloses a cyclosporin *per se*; rather, the question is, could any of the compounds disclosed be construed as a cyclosporin derivative, or would there be motivation to synthesize a compound which could be construed as a cyclosporin derivative...? The answer to both questions is in the affirmative. Consider figure 1 of the instant application. After treating CsA with acetic anhydride, $(OMe)_3BF_4$ and methoxide, one is left with an open-chain structure. If one were to remove the amide group methyl substituents, one would be left with the following, wherein "Xa1" represents (2S,3R,4R,6E)-3-acetoxy-4-methyl-2-(methylamino)-6-octenoic acid, and wherein "Xa2" represents ethylglycine:

Leu-Val-Leu-Ala-Ala-Leu-Leu-Val-Xa1-Xa2-Gly-OMe

Presumably, applicants would agree that this is a "cyclosporin derivative". Suppose next that the dipeptide at the C-terminus were removed. One would be left with the following:

Leu-Val-Leu-Ala-Ala-Leu-Leu-Val-Xa1-OH

Is this a "derivative" of cyclosporin, or is this not a "derivative" of cyclosporin...?

Suppose next that the three amino acids at the C-terminus were removed from this peptide. One would be left with the following:

Leu-Val-Leu-Ala-Ala-Leu-OH

Is this a "derivative" of cyclosporin, or is this not a "derivative" of cyclosporin...?

Suppose next that the three amino acids at the C-terminus were removed from this peptide. One would be left with the following:

Leu-Val-Leu-OH

Is this not a derivative of cyclosporin?

Thus, it becomes a question of where one wants to draw the line. The claims impose no specific structural limits on the claimed compound (apart from just one amino acid). There is no requirement for amide bonds to be N-methylated, there is no suggestion as to whether the amino acids contained in the compound might be produced by eukaryotic organisms or prokaryotic organisms, and there is no requirement that any particular biological activity be exhibited. By way of contrast, consider the following claims (claims 100-101):

> *100. A compound which obtained by replacing at least one amino acid of a naturally-occurring cyclosporin with an amino acid of formula I:..[etc.]*
>
> *101. A cyclosporin derivative in which the peptide chain comprises at least one residue of an amino acid of formula I...[etc.]*
> *.... and which cyclosporin derivative is effective to inhibit cis-trans isomerase activity of cyclophilin A.*

Claim 100 requires that the only change in structure is that of replacing one or more of the amino acids of a naturally-occurring cyclosporin with an amino acid of formula I. In claim 101, there are no structural limitations, but the claim requires that a specific biological activity be exhibited. Both of these claims would circumvent the disclosure of Wohr.

As the claims stand, however, they remain anticipated.

✺

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800